

Scientific papers

Antiphospholipid antibodies: a risk factor for occlusive ocular vascular disease in systemic lupus erythematosus and the 'primary' antiphospholipid syndrome

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SUMMARY Seven cases of occlusive ocular vascular disease affecting retinal and choroidal vessels were found among 84 consecutive patients with raised levels of anticardiolipin antibodies attending the lupus arthritis clinic at St Thomas's Hospital from 1985 to 1987. Six patients with systemic lupus erythematosus (SLE) and one with a 'primary antiphospholipid syndrome' had occlusive ocular vascular disease affecting a variety of vessels. This gives a prevalence of occlusive ocular vascular disease of 8% in this subgroup of patients, significantly higher than the 0.5–2.0% previously reported in patients with SLE. Four of these patients also suffered from cerebrovascular disease and central nervous system disease in SLE. Additionally, other features of the antiphospholipid syndrome were frequently present. These findings suggest that patients with SLE and raised anticardiolipin antibodies have a higher risk of developing occlusive ocular vascular disease than has been previously reported.

Key words: anticardiolipin antibodies, lupus anticoagulant, retinal vein/artery thrombosis.

Ocular manifestations of systemic lupus erythematosus (SLE) include mucocutaneous involvement of the eyelids, secondary Sjögren's syndrome, optic neuropathy, and retinopathy.^{1–7} The retinopathy generally consists of cotton wool spots with or without retinal haemorrhages and may occur in the absence of hypertension. The underlying disease involves microvascular occlusion mediated by circulating immune complexes causing retinal nerve fibre layer infarction.³ The prevalence ranges from 3%¹ to 29%⁴ and depends on the patient population evaluated.

By contrast, a less common but more severe form of ocular disease in SLE is occlusive ocular vascular disease. The process is generally one of diffuse

arteriolar occlusion with extensive capillary non-perfusion, but as Jabs *et al* showed in their extensive review² a more focal vascular disease, including retinal artery or vein occlusion, may occur. After such extensive ischaemia various consequences of neovascularisation, such as vitreous haemorrhage, traction retinal detachment, and thrombotic glaucoma, may occur.² In this report we record six patients with SLE and one with a 'primary antiphospholipid syndrome', all with raised levels of anticardiolipin antibodies, who developed occlusive ocular vascular disease.

Patients and methods

Among 84 consecutive patients who attended the lupus arthritis clinic at St Thomas's Hospital from 1985 to 1987 with SLE or the antiphospholipid syndrome and raised levels of anticardiolipin anti-

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Table 1 Occlusive ocular vascular disease and antiphospholipid antibodies

Patient No	Sex	Age (years)	Diagnosis	Manifestations of APL* syndrome	Anticardiolipin antibodies		Antinuclear antibody titre	Ocular lesion
					IgG aCL†	IgM aCL†		
1	F	53	SLE*	Transient ischaemic attacks Livedo reticularis Valve lesion (MI)* Cerebral infarctions (2) Thrombocytopenia	Medium	—	+ 1/320	Central retinal artery occlusion
2	F	38	SLE	Transient ischaemic attacks Cerebral infarctions Multiple abortions Livedo reticularis Thrombocytopenia	Medium	—	+ 1/40	Choroidal vascular occlusions (multiple)
3	F	33	SLE	—	—	Medium	—	Choroidal vascular occlusions (multiple)
4	F	33	SLE	Left subclavian thrombosis Guillain-Barré syndrome Recurrent cerebral infarctions Multi-infarct dementia Deep vein thrombosis Pulmonary emboli Livedo reticularis	High	Low	+ 1/640	Retinal vein occlusion
5	M	49	Primary APL syndrome	Multi-infarct dementia Cortical blindness Thrombocytopenia	High	—	+ 1/20	Thrombotic glaucoma
6	F	52	SLE	Aortic valve lesion	Medium	—	+ 1/160	Retinal artery occlusion
7	F	28	SLE	Thrombocytopenia Miscarriage (1)	Medium	—	+ 1/160	Retinal artery occlusion

*APL=antiphospholipid; aCL=anticardiolipin; SLE=systemic lupus erythematosus; MI=mitral incompetence.

†IgG aCL: high=>80 GPL units, medium=20-80 GPL units, low=5-20 GPL units; IgM aCL: high=>50 MPL units, medium=6-50 MPL units, low=3-6 MPL units.

bodies, we identified seven patients with occlusive ocular vascular disease. These seven patients had previously undergone a full ophthalmological examination. Table 1 records their main clinical and serological characteristics. The anticardiolipin antibodies were estimated by a modified enzyme linked immunosorbent assay (ELISA) as described by Gharavi *et al.*⁸

Results

Of the 84 patients in the study, seven patients suffered from occlusive ocular vascular disease (six had SLE and one had primary antiphospholipid syndrome). Thus the prevalence of occlusive ocular vascular disease was 8% in this subgroup of patients with raised anticardiolipin antibodies. Table 1 records the ocular lesions of these patients.

Four of these patients also had cerebrovascular disease (three had SLE, one had primary antiphospholipid syndrome). Thus three of six patients (50%) with SLE and occlusive ocular vascular disease had cerebrovascular disease. Table 1 records the neurological lesions of these patients.

Six of the patients recorded displayed additional features of the antiphospholipid syndrome.

Discussion

The 8% prevalence of occlusive ocular vascular disease in the subgroup of patients we studied is significantly higher than the 0.5–2.0% previously reported in SLE.¹ This study also supports the finding in SLE of a strong association between occlusive ocular vascular disease and central nervous system involvement.²

The subject of occlusive ocular vascular disease in SLE was extensively reviewed recently by Jabs *et al.*, who documented 11 of their own patients and reviewed the studies of 21 patients previously published.² Of their own patients, seven had severe generalised retinal vaso-occlusive disease, while four had more focal vascular occlusions (central retinal artery occlusion (one), branch retinal artery occlusions (two), and central retinal vein occlusion (one)). They found that eight of their 11 patients (73%) also suffered from central nervous system lupus, which was a significantly higher prevalence than in the other publications reviewed, where the figure was 37%. No reference to antiphospholipid antibodies was made in their paper, though one of their patients was subsequently found to have anticardiolipin antibodies on testing by our laboratory. This patient had recurrent deep vein thromboses, pulmonary emboli, transient ischaemic attacks, hemiparesis, and thrombocytopenia.

The antiphospholipid antibodies (antibodies to

cardiolipin, the 'lupus anticoagulant', and the antibodies responsible for the false positive serological test for syphilis—Venereal Disease Research Laboratory test) have been associated with arterial and venous thrombosis occurring at various sites.⁹ This association, originally called the 'anticardiolipin syndrome'¹⁰ and subsequently referred to as the antiphospholipid syndrome, has been expanded to include recurrent fetal loss, a variety of neurological syndromes, and thrombocytopenia.¹¹ Livedo reticularis has also been associated.^{12–13} In comparison with the general SLE population an increased prevalence of heart valve lesions, particularly affecting the mitral and aortic valves, has recently been recorded in patients with these antibodies.^{14–16} In addition, there have been case reports where the association appears to be prominent.^{17–18} This subject has recently been extensively reviewed.¹⁹ The antiphospholipid syndrome may manifest as a primary entity in the absence of any specific autoimmune disease^{20–22} but is more commonly seen in association with SLE, or lupus-like disease (where less than four of the 1982 American Rheumatism Association criteria for the classification of SLE are met).²³

In a previous study of an unselected group of 40 patients with occlusive ocular vascular disease and no underlying connective tissue disease antiphospholipid antibodies were not found.²⁴ There have been few reports linking occlusive ocular vascular disease with antiphospholipid antibodies in SLE. The two patients reported by Hall *et al.*, both of whom demonstrated the lupus anticoagulant, represented the first definitive documentation of this association.²⁵ One of their patients had thrombocytopenia. One patient recorded by Silverman *et al.*, with a central retinal vein occlusion complicating SLE, had a prolonged partial thromboplastin time, suggesting the presence of the lupus anticoagulant.²⁶ The patient recorded by Ford *et al.* also suffered a retinal artery occlusion.¹⁷ Retinal vein thrombosis is also mentioned in several reviews on the lupus anticoagulant.^{27–29} A recent interesting paper described a woman with Sneddon's syndrome, who developed a central retinal artery occlusion in association with antibodies to phosphatidylethanolamine.³⁰ Sneddon's syndrome comprises livedo reticularis, variable cerebrovascular symptoms, and labile hypertension.³¹ The original patients described by Sneddon did not show any evidence of autoimmune disease, though immunological testing was limited in 1965. In a recent study from our unit,³² however, three of 35 patients with cerebrovascular disease and livedo reticularis were found to have antiphospholipid antibodies in the absence of SLE, and would conform to the same group of patients as described by Sneddon.

We therefore conclude that patients with SLE and raised levels of anticardiolipin antibodies have a higher risk of developing occlusive ocular vascular disease than previously reported. In our group of patients features of the antiphospholipid syndrome were frequently present and in addition there was a high prevalence of central nervous system disease, particularly stroke.

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References

- Gold D H, Morris D A, Hertrind P. Ocular findings in systemic lupus erythematosus. *Br J Ophthalmol* 1972; **56**: 800-4.
- Jabs D A, Fine S L, Hochberg M C, Newman S A, Heiner G G, Stevens M B. Severe retinal vaso-occlusive disease in systemic lupus erythematosus. *Arch Ophthalmol* 1986; **104**: 558-63.
- Jabs D A, Miller N R, Newman S A, *et al*. Optic neuropathy in systemic lupus erythematosus. *Arch Ophthalmol* 1986; **104**: 564-8.
- Lanham J G, Barrie T, Kohner E M, Hughes G R V. SLE retinopathy evaluation by fluorescein angiography. *Ann Rheum Dis* 1982; **41**: 473-8.
- Clifton F, Green C H. Ocular changes in systemic lupus erythematosus. *Br J Ophthalmol* 1955; **39**: 1-10.
- Bishko F. Retinopathy in systemic lupus erythematosus. *Arthritis Rheum* 1972; **15**: 57-63.
- Graham E M, Spalton D J, Barnard R O, Garner A, Russell R W. Cerebral and retinal vascular changes in systemic lupus erythematosus. *Ophthalmology* 1985; **92**: 444-8.
- Gharavi A E, Harris E N, Asherson R A, Hughes G R V. Anticardiolipin antibodies: isotype distribution and phospholipid specificity. *Ann Rheum Dis* 1987; **46**: 1-6.
- Asherson R A, Harris E N. Anticardiolipin antibodies—clinical associations. *Postgrad Med J* 1986; **62**: 1081-7.
- Hughes G R V, Harris E N, Gharavi A E. The anticardiolipin syndrome. *J Rheumatol* 1986; **13**: 486-9.
- Harris E N, Asherson R A, Hughes G R V. Antiphospholipid antibodies—autoantibodies with a difference. *Annual Review of Medicine* 1988; **39**: 261-71.
- McHugh N J, Maymo H, Skinner R P, James I, Maddison P J. Anticardiolipin antibodies, livedo reticularis, and major cerebrovascular and renal disease in systemic lupus erythematosus. *Ann Rheum Dis* 1988; **47**: 110-5.
- Asherson R A, Mayou S, Black M, Harris E N, Hughes E R V. Livedo reticularis, connective tissue disease, anticardiolipin antibodies and CNS complications [Abstract]. *Arthritis Rheum* 1987; **30**: S69.
- Chartash E K, Paget S A, Lockshin M D. Lupus anticoagulant associated with aortic and mitral valve insufficiency. *Arthritis Rheum* 1986; **29**: 595.
- Cronin M E, Biswas R H, Van der Straeten C, Fleisher T A, Klippel J H. IgG and IgM anticardiolipin antibodies in patients with lupus and anticardiolipin antibody associated clinical syndromes. *J Rheumatol* 1988; **15**: 795-8.
- Baguley E, Byrne C, Asherson R A, Coltart J, Hughes G R V. Valvular lesions in SLE: a possible relationship with antiphospholipid antibodies and cerebrovascular disease. *Br J Rheumatol* 1988; **27** (suppl 1): 31.
- Ford P M, Ford S E, Lillicrap D P. Association of lupus anticoagulant with severe valvular heart disease in SLE. *J Rheumatol* 1988; **15**: 597-600.
- Asherson R A, Gibson D G, Evans D W, Baguley E, Hughes G R V. Diagnostic and therapeutic problems in two patients with antiphospholipid antibodies, heart valve lesions, and transient ischaemic attacks. *Ann Rheum Dis* 1988; **47**: 947-53.
- Asherson R A, Lubbe W F. Cerebral and valve lesions in SLE in association with antiphospholipid antibodies. *J Rheumatol* 1988; **15**: 539-43.
- Asherson R A. A 'primary' antiphospholipid syndrome. *J Rheumatol* (in press).
- Harris E N, Baguley E, Asherson R A, Hughes G R V. Clinical and serological features of the 'antiphospholipid syndrome'. *Br J Rheumatol* 1987; **26** (suppl 2): 19.
- Mackworth-Young C G, David J, Loizou S, Walport M. Primary antiphospholipid syndrome: features of patients with raised anticardiolipin antibodies and no other disorder. *Br J Rheumatol* 1987; **26** (suppl 2): 94.
- Tan E M, Cohen A S, Fries J A, *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; **25**: 1271-7.
- Merry P, Acheson J F, Asherson R A, Hughes G R V. Management of retinal vein occlusion. *Br Med J* 1988; **296**: 294.
- Hall S, Buettner H, Luthra H S. Occlusive retinal vascular disease in systemic lupus erythematosus. *J Rheumatol* 1984; **11**: 846-9.
- Silverman H, Lubeck M J, Briney W G. Central retinal vein occlusion complicating systemic lupus erythematosus. *Arthritis Rheum* 1978; **21**: 839-43.
- Gastineau D A, Kazmier F J, Nichols W L, Bowie E J M. Lupus anticoagulant: an analysis of the clinical and laboratory features of 219 cases. *Am J Hematol* 1985; **19**: 265-75.
- Lechner K, Pabinger-Fasching I. Lupus anticoagulants and thrombosis. A study of 25 cases and review of the literature. *Haemostasis* 1983; **15**: 254-62.
- Vermeylen J, Blockmans D, Spitz B, Deckmyn H. Thrombosis and immune disorders. *Clin Haematol* 1986; **15**: 1-17.
- Jonas J, Kolble K, Volker H E, Kalden R. Central retinal artery occlusion in Sneddon's disease associated with antiphospholipid antibodies. *Am J Ophthalmol* 1986; **102**: 37-40.
- Sneddon I B. Cerebrovascular lesions and livedo reticularis. *Br J Dermatol* 1965; **77**: 180.
- Asherson R A, Khamishta M, Baguley E, *et al*. Cerebrovascular disease and antiphospholipid antibodies. *Am J Med* (in press).